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(54) Novel synthesis of 19-nor vitamin D compounds.

(57) A convergent synthesis of 19-nor-vitamin D compounds, specifically 19-nor-1α,25-dihydroxyvitamin D_3, is disclosed. The synthesis can also readily be utilized for preparing other 1α-hydroxylated 19-nor-vitamin D compounds. The key step in the synthesis is a suitable application of Lythgoe's procedure i.e. a Horner-Wittig reaction of the lithium anion of a phosphine oxide with a Windaus Grundmann ketone to give, after any necessary deprotection, the desired 19-nor-vitamin D compound.

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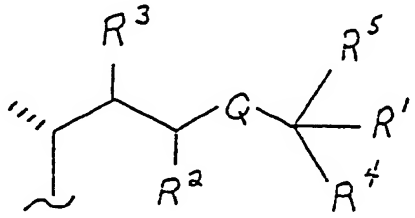
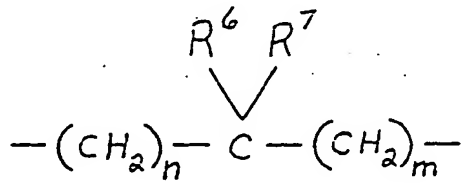
mura, J. Org. Chem. 48, 1414 (1983); E. G. Baggiolini et al., J. Org. Chem. 51, 3098 (1986): Sardina et al., J. Org. Chem. 51, 1264 (1986); J. Org. Chem. 51, 1269 (1986)].

Another important aspect of this invention is the preparation of ring-A units of general structure I from (-) quinic acid. In structure I, above, X^1 and X^2, which may be the same or different, represent hydroxy-protecting groups, and Y represents a grouping that renders the hydrogen on the adjacent carbon center sufficiently acidic to yield a reactive carbanion upon treatment with a strong base. Exemplary of such groupings Y are $-P(O)Ph_2$, $-P(O)(OAlkyl)_2$, $-SO_2Ar$, or $-Si(Alkyl)_3$. Compounds of type I, above, are new. Their synthesis, and other novel intermediates used in their preparation are disclosed herein.

In the bicyclic-ketone of structure II, or in the 19-nor-vitamin D compound of structure III, above, the substituent R may represent any desired group, it being understood that any functionalities in R that might be sensitive, or that interfere with the condensation reaction, be suitably protected as is well-known in the art. More specifically, R may represent, for example, hydrogen, alkyl, hydroxyalkyl, deuteralkyl, fluoroalkyl, or a side chain of the formula



where R^1, R^2, R^3, independently represent hydrogen, hydroxy, protected hydroxy, or alkyl, where the bond between carbons 22 and 23 may be a single, double or triple bond, where Q is the group

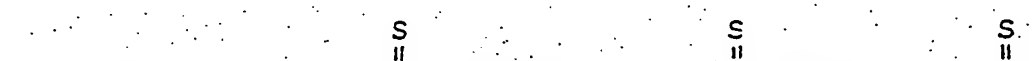


where R^6 and R^7, independently, are selected from hydrogen, alkyl, hydroxyalkyl, hydroxy, protected hydroxy, and fluoro, or where R^6 and R^7 taken together represent an oxo group or an alkylidene group, and where n and m are integers having, independently, the values 0, 1, 2, 3, 4 or 5,
where R^4 and R^5, independently, represent deuteroalkyl, fluoroalkyl and the group Q-H, or R^4 and R^5, taken together, represent the group Q, with the proviso that at least one of n or m has the value of 1 or greater, and wherein the carbon at any one of positions 20, 22 or 23 in the side chain may be replaced by an O, S, or N atom.

As used in the description, and in the claims, the term "hydroxy-proteting group" refers to any group commonly used for the protection of hydroxy functions during subsequent reactions, including, for example, acyl or alkylsilyl groups such as trimethylsilyl, triethylsilyl, t-butyldimethylsilyl and analogous alkyl or arylsilyl radicals, or alkoxyalkyl groups such as methoxymethyl, ethoxymethyl, methoxyethoxymethyl, tetrahydrofuranyl or tetrahydropyranyl. A "protected-hydroxy" is a hydroxy function derivatized by one of the above hydroxy-protecting groupings. "Alkyl" represents a straight-chain or branched hydrocarbon radical of 1 to 10 carbons in all its isomeric forms, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, etc., and the terms "hydroxyalkyl," "fluoroalkyl" and "deuteroalkyl" refer to such an alkyl radical substituted by one or more hydroxy, fluoro or deuterium groups respectively. An "acyl" group is an alkanoyl group of 1 to 6 carbons in all its isomeric forms, or an aroyl group, such as benzoyl, or halo-, nitro- or alkyl-substituted benzoyl groups, or an alkoxycarbonyl group of the type Alkyl-O-CO-, such as methoxycarbonyl, ethoxycarbonyl, propyloxycarbonyl, etc., or a dicarboxylic acyl group such as oxalyl, malonyl, succinoyl, glutaroyl, or adiopoyl. The term "aryl" signifies a phenyl-, or an alkyl-, nitro- or halo-substituted phenyl group. The term alkoxy signifies the group alkyl-O-. Keton es of general structure II featuring homologated side chains are new compounds.

Ketones of structure II, with diverse side chain groups R, can be prepared by known methods, as documented, for example by Baggiolini et al., J. Org. Chem. 51, 3098 (1951); Baggiolini et al., U.S. Patent 4,804,502; Sardina et al., J. Org. Chem. 51, 1264 (1986); Kocienski et al., J. Chem. Soc. Perkin Trans. 1, 834 (1978); Toh

It has been found that intermediate IV in all of the above described structural modifications can be used for the reductive removal of the C-4-hydroxy group, by means of a free radical deoxygenation procedure [Barton and McCambie, J. Chem. Soc. Perkin trans. 1, 1574 (1975); Robins et al., J. Am. Chem. Soc. 103, 933 (1981); 105, 4059 (1983); Barton and Motherwell, Pure & Appl. Chem., 53, 15 (1981)]. This process entails the conversion of the free C-4-hydroxy group in compound IV to a suitable derivative, for example, a thiono-ester or xanthate derivative, as represented by general structure V in the above reaction scheme, where X^3 is

a grouping such as 

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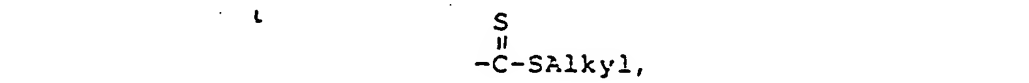


and where A, B, X^1 and X^2 have the meaning previously defined. Intermediates of type V, upon treatment with a hydrogen radical source in the presence of a radical initiator, then undergo reductive deoxygenation to furnish compounds of general structure VI, where A, B, X^1 and X^2 represent substituents as previously defined. For such deoxygenation reactions, suitable sources of hydrogen radicals are the trialkyltin hydrides (e.g. tributyltin hydride) or tris(trialkylsilyl)silanes (e.g. $(Me_3Si)_3SiH$) [Schummer and Hofle, Syn. Lett. 106 (1990); Ballestri et al., J. Org. Chem. 56, 678 (1991)], and suitable radical initiators are provided by azaisobutyronitrile (AIBN) or by irradiation. It is to be noted that the substituents A, B, X^1 and X^2 remain unchanged during the above described two-step deoxygenation procedure. Thus, from compound IV, where A is -COOAlkyl and B is -OH, there is obtained compound VI, where A is -COOAlkyl, and B is -OH, and likewise, compound IV, where A and B, taken together represent =O; or =CHCOOAlkyl, yields compound VI, where A and B together, represent =O, or =CHCOOAlkyl, respectively.

As in the case of the compounds of structure IV, it is possible to effect transformations of the A and B substituents of the compounds of structure VI by processes entirely analogous to those discussed in connection with the compounds of structure IV. Thus, compound VI, where A is COOAlkyl and B is hydroxy, upon ester reduction and vicinal diol cleavage, as described above for the case of compound IV, provides VI as the cyclohexanone analog, where A and B, taken together represent an oxo group, and the latter, upon alkylation as described above, yields the cyclohexylidene modification, i.e. VI, where A and B taken together represent =CHCOOAlkyl.

For the subsequent steps towards the preparation of ring A-synthon of general structure I, the cyclohexylidene ester VI, where A and B together represent =CHCOOAlkyl, and X^1 and X^2 signify hydroxy-protecting groups, is the desired intermediate. These subsequent steps comprise, first, the reduction of the ester (using, for example, $LiAlH_4$ or diisobutylaluminum hydride, DIBAL-H) to the corresponding primary alcohol of structure VII, shown below, where X^1 and X^2 represent hydroxy-protecting groups, and Y^1 is hydroxy. This alcohol, under conventional tosylation or mesylation conditions, may be transformed to the corresponding tosylate or mesylate, structure VII, where Y^1 represents $-O-SO_2PhMe$, or $-OSO_2Me$, or, alternatively, the alcohol may be subjected to displacement by halogen, to obtain the corresponding halide, structure VII, where Y^1 is a halogen atom, i.e. I, Br or Cl. From the mesylate, tosylate or halide of structure VII, the desired synthon of structure I is now obtained by various generally known conversion reactions. Thus, the halide, tosylate or mesylate, upon treatment with a metal diphenylphosphide and subsequent peroxide oxidation, yields the desired phosphine oxide derivative of structure I, where $Y=-P(O)Ph_2$. Similarly, the halide upon treatment with triethylphosphite under Arbuzov reaction conditions, provides the corresponding phosphonate derivative I, where $Y=-P(O)(OEt)_2$. From the tosylate or mesylate, upon displacement with the sodium salt of an arylsulfinic acid, there can be obtained the aryl-sulfone derivative of compound I, where $Y=-SO_2Ar$. Likewise, upon reaction of the halide VII with trichlorosilane followed by alkylation with an alkylhalide, there is obtained the alkylsilane derivative of compound I, where $Y=-Si(Alkyl)_3$.

The condensation reaction is advantageously conducted by treating the ring A unit of general structure I, dissolved in an organic solvent, with a strong base (e.g. an alkali-metal hydride, alkyl- or aryl lithium, or a lithium alkylamide reagent), so as to generate the anion of I, and then allowing this anion to react with ketone I, so as to achieve condensation to the 19-nor-vitamin analog III, either directly, or via intermediates (e.g. in the case

=CHCOOAlkyl, and of which specific embodiments are illustrated by structures 6, 7, 8, and 9 in Scheme I. Likewise, new are 4-deoxy intermediates of structure VI, above, where A is COOAlkyl, -CH_2OH, B is OH, or where A and B, together, represent an oxo group, which examples are provided by structures 14, 15, and 16 in Scheme II. It is also important to note that although these intermediates are generally used in their hydroxy-protected form in the various processes discussed above, the hydroxy-protecting groups (X^1, X^2, X^3) may also be removed, under conditions known in the art, to obtain the corresponding free-hydroxy-intermediates (compounds I, IV, V, VI and VII, where X^1 and/or X^2 and/or X^3 represent H) or be replaced by alternative hydroxy-protecting groups.

In Scheme IV is outlined a specific embodiment of the condensation reaction between phosphine oxide 12 (Scheme I) and a suitable ketone (structure 18) representing rings C and D plus sidechain of the desired 19-nor-vitamin compound. The phosphine oxide 12 was treated with base (butyllithium) at low temperature in tetrahydrofuran to generate the corresponding phosphinoxy anion, which was allowed to react with the hydroxy-protected ketone 18 [Baggiolini et al., J. Org. Chem. 51, 3098 (1986)] to give the desired 19-nor-vitamin derivative 19, from which, after protecting-group removal under conventional conditions, there was obtained crystalline 1α,25-dihydroxy-19-norvitamin D_3 (20).

Example 1

(a) (1R,3R,4R,5R) Methyl 3,5-Bis (tert-butyldimethylsilyloxy)-1,4-Dihydroxycyclohexane-Carboxylate (2)

p-Toluene sulfonic acid (0.5 g) was added to a solution of quinic acid 1 (12.74 g, 66.3 mmol) in methanol. The solution was stirred for 24 h. Solid NaHCO3 (1.0 g) was added and after 15 min the solution was filtered and concentrated to give 12.61 g (62.16 mmol) of the methyl ester in 92% yield.

tert-Butyldimethylsilyl chloride (6.73 g, 44.62 mmol) was added to a solution of methyl (1R,3R,4R,5R) (-) quinate (3.68 g, 17.85 mmol) and triethylamine (6.2 mL, 44.62 mmol) in 44 mL of anhydrous dimethyl formamide at 0°C with stirring. After 4 h the solution was warmed to room temperature and stirring continued for another 14 h. The solution was poured into water and extracted with ether. The combined organic layers were extracted with brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography on silica gel, eluting with 5-10% ethyl acetate in hexane mixtures, to give 4.6 g (60%) of 2 as a white solid. M.p. 82-82.5°C (after recrystallization from hexanes). ^1H NMR ($CDCl_3$, 500 MHz) δ 4.53 (bs, 1 H), 4.36 (bs, 1H), 4.11 (ddd, 1H), 3.76 (s, 3H), 3.42 (dd, 1H), 2.31 (bs, 1H), 2.18 bd, 1H), 2.05 (ddd, 2H), 1.82 (dd, 1 H), 0.91 (s 9 H), 0.89 (s, 9 H), 0.15 (s, 3 H), 0.14 (s, 3 H), 0.11 (s, 3 H), 0.09 (s, 3 H). MS m/e (relative intensity) 377 (70), 227 (91).

(b) (1R,3R,4R,5R) [3,5-Bis (tert.-butyldimethylsilyloxy)-1,4-dihydroxy]-1-hydroxymethyl cyclohexane (3).

Diisobutyl aluminum hydride (45 mL, 45.0 mmol , 1.0 M in hexanes) was added to a solution of the ester 2 (3.26 g, 7.5 mmol) in ether (45 mL) at -78°C. After 20 min. the solution was warmed to -23°C and stirred for 2 h. The solution was diluted with ether and then 2 N potassium sodium tartrate was slowly added. The solution was warmed to room temperature and stirred for 15 min. The ether layer was separated and the aqueous layer extracted with ether. The combined ether layers were extracted with brine, dried over anh. $MgSO_4$, filtered and concentrated. The material was further purified by column chromatography on silica gel with 25% ethyl acetate/hexanes to give 83% of 3 (2.52 g, 6.20 mmol), Mp. 108-109°C from hexanes. 1H NMR ($CDCl_3$, 500 MHz) δ 4.52 (bs, 1 H), 4.12 (ddd, 1 H) 3.40 (dd, 1 H) (dd, 2 H), 2.28 (d, 1 H) 2.11 (dd, 1 H) 2.00 (ddd, 2 H), 1.52 (dd, 1 H), 1.33 (dd, 1 H) 0.91 (s, 9, H) 2.00 (ddd, 2 H), 1.52 (dd, 1 H), 1.33 (dd, 1 H), 0.91 (s, 3 H), 0.11 (s, 3 H). MS m/e (relative intensity) : 349 (8), 331 (13), 239 (12), 199 (100).

(c) (3R,4R,5R) [3,5-Bis (tert.-butylc:methylsilyloxy)-4-hydroxy]-1-cyclohexanone (4).

Sodium periodate saturated water (28.5 mL) was added to the triol 3 (1.91 g, 4.7 mol) in methanol (124 mL) at 0°C. The solution was stirred for 1 h, then poured into water and extracted with ether. The combined ether fractions were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated to give 1.72 g (4.59 mmol) of 4 (98%). No further purification was required. Mp. 98-100°C from hexanes. ^1H NMR ($CDCl_3$, 500 MHz) δ 4.28 (m, 2 H), 3.80 (bs, 1 H), 2.77 (dd, 1 H, J=14.3, 3.4 Hz), 2.59 (dd, 1H, J=13.1, 10.7 Hz), 2.45 (dd, 1 H, J=14.1, 5.2 Hz) 2.25 (bd, 1 H, J=15.9 Hz), 0.90 (s, 9 H), 0.85 (s, 9H), 0.08 (s, 34 H), 0.08 (s, 3 H), 0.06, (s, 6 H). MS m/e (relative intensity) 317 (62), 231 (16), 185 (76), 143 (100).

(85), 211 (83), 171 (100).

(i) (3R,5R)[3,5-Bis(tert.-butyldimethylsilyloxy)-cyclohexylidene]-1-chloroethane (11)

A solution of 50mg (0.37 mmol) N-chlorosuccinimide in 2 mL of anhydrous dichloromethane was treated at 0°C under argon with 30 µL (0.41 mmol) dimethyl sulfide. A white precipitate formed. The mixture was stirred an additional 15 min. at 0°C. then cooled to -25°C and treated with 50 mg (0.13 mmol) of the alcohol 10 dissolved in 0.5 mL of anhydrous dichloromethane. The mixture was stirred under argon for 30 min. at -20°C and then at 0°C for 30 min. The reaction mixture was poured on ice, and extracted with ethyl acetate. The organic phase was washed with brine, dried over anhydrous $MgSO_4$ filtered and evaporated. The residue was purified by fast filtration through a silica gel column, eluting with 5% ethyl acetate in hexane to give 52 mg (quant) of the chloro compound 11. ^1H NMR ($CDCl_3$ 500 MHz), δ 0.06 (s, 12 H), 0.89 (s, 18 H), 1.73 (br dd, 1 H), 2.22 (m, 1 H) 2.30 (m, 1 H), 2.32 (m, 1 H), 4.04 (dd, J=7.3, 10.8 Hz, 2 H), 4.11 (dd, J=2.87, 10.46 Hz, 2 H), 5.51 (brt 1 H). MS m/e (relative intensity) : 237 (93), 215 (52), 189 (79), 105 (100).

(j) (3R,5R)-[Bis(tert.-butyldimethylsilyloxy)-cyclohexyli-denelethyl-diphenylphosphine oxide (12).

40 µL (60 µmol) n.Butyl lithium (1.5 M in hexanes) was added to 10 µL (60 µmol) diphenylphosphine in 30 µL anhydrous tetrahydrofuran at 0°C with stirring under argon. The orange solution was treated at 0°C with 20 mg (50 µmol) of the allylic chloride 11 in 300 + 200 µL anhydrous tetrahydrofuran. The resulting yellow solution was stirred an additional 40 min at 0°C and quenched by the addition of water. Solvents were evaporated under reduced pressure and the residue was dissolved in chloroform. The chloroform layer was shaken twice with 5% hydrogen peroxide. The chloroform layer was separated and washed with aqueous sodium sulfite, water and brine, dried over anhydrous $MgSO_4$, filtered and evaporated. The residue was dissolved in 20% 2-propanol in hexane and passed through a silica SepPak and purified by HPLC (Zorbax-Sil 9.4 x 25 cm column, 20% 2-propanol in hexane) to give 5.5 mg (22%) of the phosphine oxide 12.

UV (EtOH):λ_{max}258.265.272 nm, ^1H NMR ($CDCl_3$, 500 mHz) δ 0.01 (ms. 12 H), 0.85 (m s, 18 H) 1.65 (m, 2 H), 1.91 (m, 1 H) 2.00 (m, 1 H), 2.22 (br d J=3.2 Hz 1 H). 3.05 (dt, J=8.5, 14.9 Hz, 1 H) 3.14 (dt, J=8.5, 14.9 Hz, 1 H), 3.98 (br s 1 H), 5.28 (q, 1 H), 7.46 (m, Ar-5 H), 7.73 (m, Ar-5 H). MS m/e (relative intensity) : 570 (M+, 1) 513 (100), 381 (46), 306 (20), 202 (55), 75 (20).

Example 2

(a) (1R,3R,4R,5R) Methyl [3,5-Bis(tert.-butyldimethylsilyloxy)1-hydroxy-4-imidaz olylthiocarbonyloxy-cyclo-hexanone carboxylate (13)

1,1'-Thiocarbonyldiimidazole (0.7 g, 4.0 mmol) was added to a solution of the 1,3-protected methyl quinate 2 (1.1 g, 2.5 mmol) in methylene chloride (10 mL). The solution was stirred at RT for 70 h. The solution was concentrated and purified by column chromatography on silica gel and the product eluted with hexane ethyl acetate mixtures to give 13 (1.2 g, 90%). ^1H NMR ($CDCl_3$, 500 MHz) δ 0.02 (s, 3H), 0.07 (s, 3H), 0.09 (s, 3H), 0.14 (s, 3H), 0.77 (s, 9H), 0.91 (s, 9H), 2.03 (m, 2H), 2.28 (m, 2H), 3.80 (s, 3H), 4.43 (br, s, 1H), 4.58 (m, 1H), 4.66 (br, s, 1H), 5.52 (dd, 1H, J=2.71, 9.05 Hz), 7.06 (d, 1H, J=1.49 Hz), 7.64 (d, 1H, J=2.76 Hz), 8.38 (s, 1H).

(b) (1R,3R,5R) Methyl [3,5-Bis(tert.-butyldimethylsilyloxy)-1-hydroxycyclohe xane carboxylate (14)

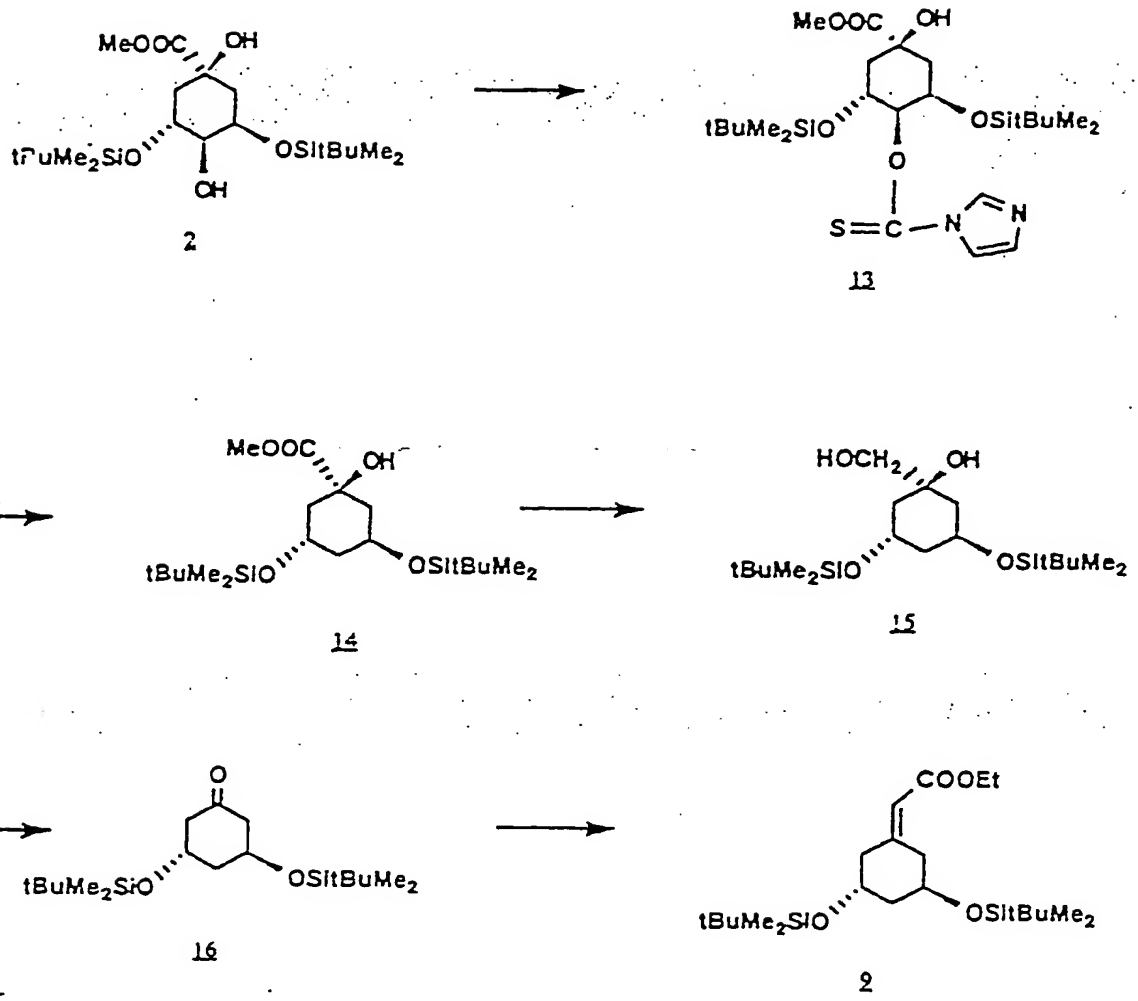
Tributyltin hydride (0.72 mL, 2.66 mmol) was added to a solution of AIBN (17 mg), and the thionoimidazole 13 (0.58 g, 1.06 mmol) in degased toluene (106 mL). The solution was heated with stirring to 100°C for 2 h and then concentrated. The residue was further purified by column chromatography on silica gel eluting with hexane, followed with 3% and 25% ethyl acetate in hexane to obtain 14 (0.322 g, 71%). ^1H NMR ($CDCl_3$, 500 MHz) δ 0.09 (s, 3H), 0.11 (s, 3H), 0.14 (s, 3H), 0.15 (s, 3H), 0.89 (s, 9H), 0.91 (s, 9 H), 1.46 (m, 2H), 1.56 (m, 1H), 1.82 (dd, 1H), 2.42 (d, J=12.21 Hz), 2.51 (d, J=13.39 Hz), 3.69 (s, 3H), 4.17 (br, s, 1H), 4.25 (m, 1H).

(c) (1R,3R,5R)-[3,5-Bis(tert.-butyldimethylsilyoxy)-1-hydroxy-1-hydroxymethylcyclohexane (15)

Diisobutyl aluminum hydride (6 mL, 9 mmol, 1.5 M in toluene) was added to a solution of the ester 14 (0.56 g, 1.3 mmol) in anhydrous toluene (20 mL) at -78°C. After 20 min the solution was warmed to 0°C and stirred for 1 h. The solution was slowly quenched by adding to a stirred 0°C solution of 2N potassium sodium tartrate. Ethyl acetate was added and the organic layer separated and the water phase extracted with ethyl acetate.

(3H, s, 18-CH_3), 0.92 (3H, d, J=6.9 Hz, 21-CH_3), 1.21 (6H, s, 26 & 27-CH_3), 4.02 (1H, m, 3α-H), 4.06 (1H, m, 1β-H), 5.83 (1 H, d, J=11.6 Hz, 7-H), 6.29 (1H, d, J=10.7 Hz, 6-H). UV (in EtOH): λ_{max}: 243, 251.5, 261nm. Mass spectrum m/e (relative intensity) : 404 (M+, 100), 386 (41) 371 (20), 275 (53), 245 (51), 180 (43), 135 (72), 95 (82), 59 (18). UV (EtOH) λ_{max}: 243, 251.5, 261 (ε 31,300, 34,600, 24,900).

Scheme II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OH
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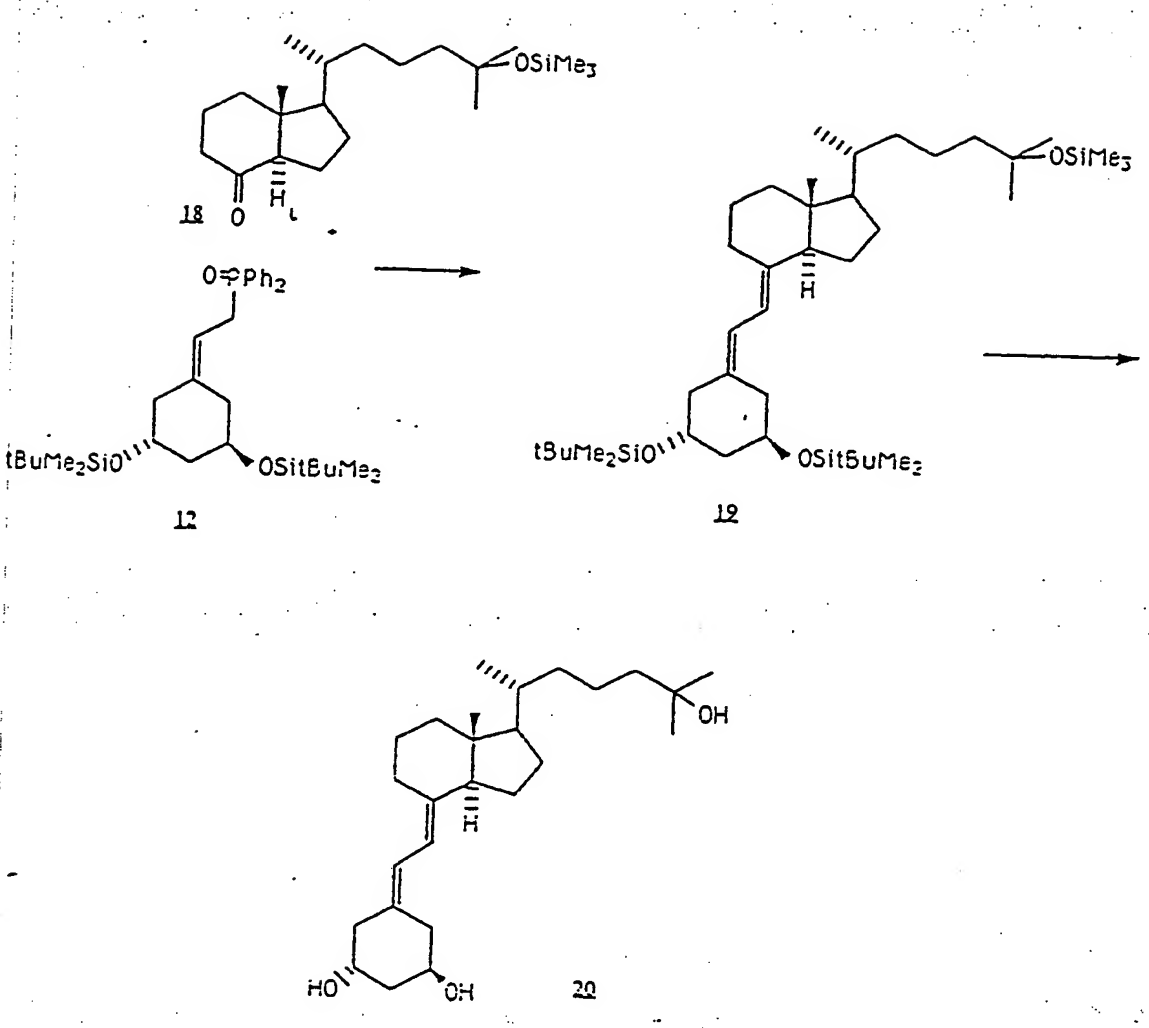
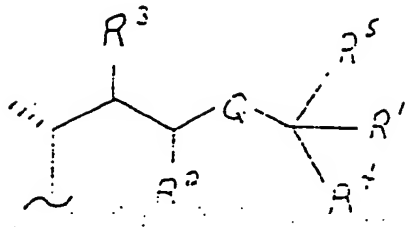
Scheme IV

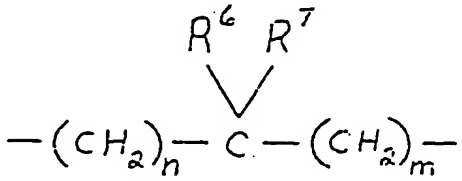


Claims

1. A method of making a 19-nor-vitamin D compound of the formula:



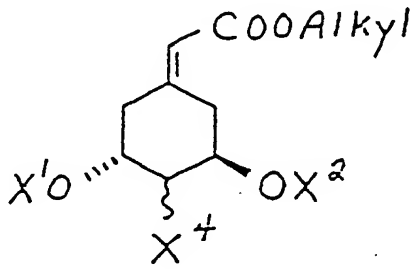
where each of R^1, R^2 and R^3, which may be the same or different, is hydrogen, hydroxy, protected hydroxy, or alkyl, where the bond between carbons 22 and 23 may be a single, double or triple bond, Q is the group



where each of R^6 and R^7, which may be the same or different, is hydrogen, alkyl, hydroxyalkyl, hydroxy, protected hydroxy or fluoro, or R^6 and R^7 taken together represent an oxo group or an alkylidene group, and each of n and m, which may be the same or different, is 0, 1, 2, 3, 4 or 5, each of R^4 and R_5, which may be the same or different, is fluoroalkyl or the group Q-H, or R4 and R^5, taken together, represent the group Q, with the proviso that at least one of n or m is 1 or more and wherein the carbon at any one of positions 20, 22 or 23 in the side chain may be replaced by an O, S or N atom.

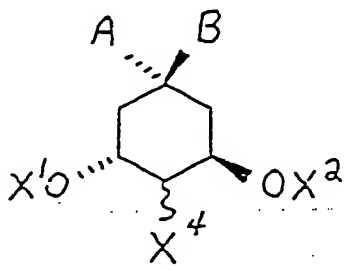
6. A method according to any one of the preceding claim for producing 19-nor-α.25-dihydroxyvitamin D_3 or 19-nor-1α-hydroxyvitamin D_3.

7. A compound of the structure:



where each of X^1 and X^2, which may be the same or different, is hydrogen or a hydroxy-protecting group, and X^4 is hydrogen, hydroxy, or protected hydroxy.

8. A compound of the structure:



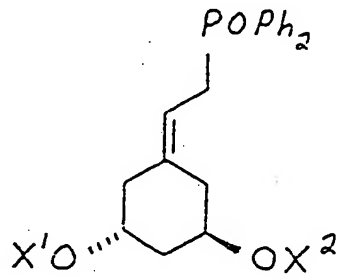
where each of X^1 and X^2, which may be the same or different, is hydrogen or a hydroxy-protecting group.

where X^3 is $-\overset{S}{\overset{\|}{C}}-OAr$, $-\overset{S}{\overset{\|}{C}}-OAlkyl$, $-\overset{S}{\overset{\|}{C}}-$imidazolyl, $-\overset{S}{\overset{\|}{C}}-S-$Alkyl, or

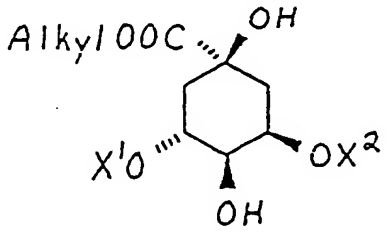
$$-\overset{S}{\overset{\|}{C}}-S-Ar,$$

in the presence of a hydrogen radical source and a radical initiator.

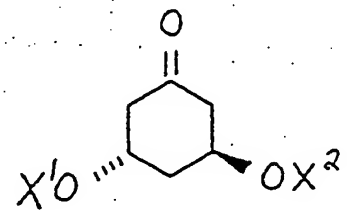
13. A method of making a phosphine oxide of the formula:



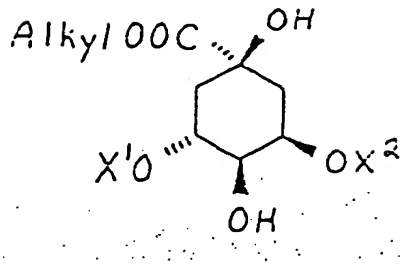
wherein each of X^1 and X^2, which may be the same or different, is hydrogen or a hydroxy-protecting group which comprises eliminating the 4-hydroxyl group of a quinic acid of the formula:



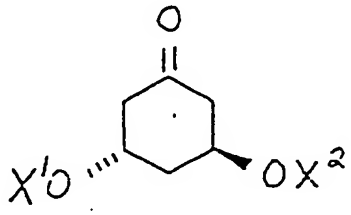
where each of X^1 and X^2, which may be the same or different, is a hydroxy protecting group, converting the resulting dehydroxylated compound to a ketone of the formula:



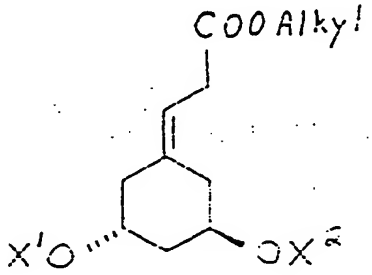
wherein X^1 and X^2 are as defined above, condensing the ketone to produce an ester of the formula:



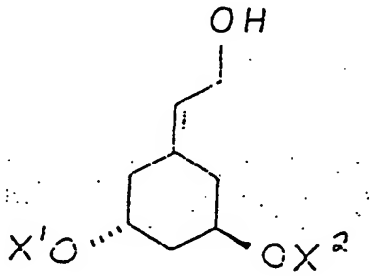
where each of X^1 and X^2, which may be the same or different, is a hydroxy protecting group, converting the resulting dehydroxylated compound to a ketone of the formula:



where X^1 and X^2 are as defined above, condensing the ketone to produce an ester of the formula:



where X^1 and X^2 are as defined above, reducing said ester to produce an alcohol of the formula:



where X^1 and X^2 are as defined above, and converting said alcohol to said compound of formula X.